Prion immunoreactivity in appendix before clinical onset of variant Creutzfeldt-Jakob disease

David A Hilton, Edward Fathers, Philip Edwards, James W Ironside, John Zajicek

A variant of Creutzfeldt-Jakob disease (CJD) was identified in 1996; there is evidence for a link between variant CJD and bovine spongiform encephalopathy (BSE). The proportion of the population exposed to infectious amounts of the BSE agent through consumption of infected meat is unknown, therefore it is difficult to predict the number of future cases of variant CJD. Prion protein (PrP) has been found in the tonsillar tissues from sheep infected with scrapie, and at necropsy from a patient with variant CJD. We describe our findings in an appendix, removed 8 months before the onset of disease, from a patient with variant CJD.

A 45-year-old man developed numbness of his face and right hand in May, 1996. Investigations included T2-weighted cranial magnetic-resonance imaging (MRI) which showed three small high-signal white-matter lesions. Multiple sclerosis was suspected. His sensory disturbances spread to his trunk and legs. He was treated for depression in April, 1997. Later that year he became hyperactive, disinhibited, and had aggressive outbursts. He also had intermittent deafness. In November, 1997, he had difficulty writing, slurred speech, and ataxia. A repeat MRI was unchanged. Visual evoked responses and examination of cerebrospinal fluid were normal. By early in 1998, his ataxia had deteriorated and his symptoms led to assessment in a psychiatric unit. Although systemic markers for vasculitis were negative, a brain biopsy was done in April, 1998, to exclude this treatable condition. Brain biopsy showed changes of variant CJD with scattered small cortical plaques surrounded by vacuoles and immunocytochemistry (with monoclonal anti-PrP antibodies 3F4 and KG9) showed extensive PrP deposition within plaques, and around neurons and blood vessels.

In September, 1995, he had had an appendectomy after 2 days of right iliac-fossa pain and fever. Histology of the appendix did not show acute appendicitis. Immunocytochemistry in May, 1998, with monoclonal antibodies 3F4 and KG9, showed immunoreactivity for PrP in the cytoplasm of scattered cells, predominantly in germinal centres (figure A). No staining was seen after omission of antibodies. The morphology of these immunoreactive cells suggested that they were follicular dendritic cells, which was confirmed by double labelling with antibodies to CD21, which co-localised to PrP immunoreactive cells (figure B). Immunoreactivity for PrP was not seen in any of 10 control appendices investigated. Demonstration of PrP within the cytoplasm of follicular dendritic cells of the appendix mirrors the findings in tonsillar lymphoid tissue. Involvement of the tonsillar tissue before onset of disease has been shown from the age of 10 months in sheep infected with scrapie; however, our findings are the first demonstration of PrP in tissue in human beings during the incubation period of CJD. Involvement of gut-associated lymphoid tissue before the clinical onset of disease is in keeping with an enteric route of entry for the variant CJD agent.

An implication of the presence of PrP in the appendix during the incubation period of variant CJD is that it offers the opportunity for large scale screening of appendectomy and, presumably, tonsillectomy, specimens removed since the onset of the BSE epidemic. Appendectomy specimens are routinely sent for histological examination and are usually available for further study. Although the incidence of human exposure to the BSE agent may be small, approximately 44 000 appendectomies are done in the UK each year (data from Royal College of Surgeons). Such a study would provide new data on the proportion of the
population at risk of developing variant CJD, although it is not known at what stage during the incubation period of variant CJD that lymphoid tissue becomes involved or whether this involvement will inevitably lead to the development of neurological disease.


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Epidermal mosaicism producing localised acne: somatic mutation in FGFR2

Colin S Munro, Andrew O M Wilkie
See commentary page 668

A 14-year-old boy with otherwise unremarkable acne for 2 years presented because the acne was much more severe in a lesion extending down his left arm (figure). His linear and atypically distal distribution, with a comedone in virtually every follicle of the affected area, suggests an unusual pathological basis. Disorders following this kind of linear or whorled pattern (lines of Blaschko) are thought to reflect the epidermal distribution of somatic mosaicism, whether due to X-inactivation in females carrying X-linked dominant mutations, or to mutation in embryonic precursors of the keratinocyte lineage. Supporting this theory, somatic mutations of the keratin gene (K10) have been detected in naevoid epidermolytic hyperkeratosis. In considering candidate genes for somatic mutation in our patient, we recalled the atypical generalised acne seen in Apert syndrome. This complex congenital malformation, characterised by craniosynostosis and syndactyly, is due to specific germline mutations in the gene for fibroblast growth factor receptor 2 (FGFR2). We examined this patient's epidermal naevus for comparable somatic mutations in FGFR2.

DNA was extracted from peripheral blood lymphocytes, from scrapings and keratinous plugs of lesional epidermis, and from banal follicular keratoses on the other arm. Scrapings routinely yielded 200–500 ng high-quality DNA. The region of FGFR2 containing the two major Apert syndrome mutations was amplified by PCR and digested with MboI and BglII, each of which has a single restriction site in the normal sequence abolished by the major Apert syndrome mutations 934C→G and 937→G, respectively. All samples showed normal digestion with BglII, but samples from lesional skin were partially resistant to MboI digestion whereas samples from the opposite arm and blood digested normally with MboI (figure). We cloned the PCR product and sequenced eight independent MboI-resistant clones. All contained the 934C→G mutation (predicting a Ser252Trp substitution) identical to that in Apert syndrome. This was confirmed by blot hybridisation of the PCR product with a mutant oligonucleotide (figure). From two independent samples of the lesion, 56% and 34%, respectively, of cells were mutated (not shown).

We conclude that the acneiform naevus is due to a somatic mutation of FGFR2 identical to one which, if present in the germline, causes Apert syndrome. The germline mutation exhibits several unusual properties, including a very high mutation rate, exclusive paternal origin, and association with advanced paternal age. The hypothesis that the mutation confers a selective advantage to male germ cells might also apply to mutant epidermal cells. Other germline mutations of FGFR2 and FGFR3 are associated with acanthosis nigricans and cutis gyrata,
in mice a dominant negative FGFR2 transgene caused epidermal thickening. 1 Hence somatic FGFR mutations may be an important cause of epidermal naevi. The mutations may differ from those of known syndromes, because defects lethal in the germline may survive in mosaic form. 1 In contrast to K 10, expressed only in epidermis, FGFR genes are widely expressed and are thus good candidates for somatic mutation in epidermal naevus syndromes, in which naevi are associated with skeletal or other abnormalities. 1 Our simple non-invasive method of selectively enriching mutant DNA from epidermal naevi provides an opportunity to test these possibilities.

We thank S Walsh for technical help, S L T Hein for generous access to clean laboratory facilities, D R McLellan for histological analysis, and D J Weatherall for support. This work was funded by a Wellcome Trust Senior Research Fellowship in Clinical Science (A O M Wilkie).


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Shuttle-walk test to assess chronic heart failure
SD Keell, JS Chambers, DP Francis, DF Edwards, RH Stables

In patients with chronic heart failure, measurement of maximum oxygen uptake (VO2 max) is widely used to assess functional capacity, prognosis, and response to treatment. This investigation involves the use of a static-exercise machine with on-line analysis of respiratory gases. The test can be bewildering and uncomfortable for patients; the gas analysis equipment is expensive to purchase and maintain, and trained staff are required. Exercise tests in athletes, based on timed shuttle runs, to and fro over a 20 m course are associated with measurements of VO2 max. Singh et al have developed a 10 m shuttle-walk test (SWT) to assess patients with chronic airways disease and permanent pacemaker implants. Two cones are placed 9 m apart and patients walk and to and fro turning outside the cones. A cassette-tape recording gives instructions to patients and controls the progress of the test with a series of beeps. Patients are required to walk such that they complete a turn as each beep sounds. The test is progressive and maximal. The walking speed increases over stages lasting 1 min and the test is terminated when a patient fails to maintain the required pace. The number of shuttles completed is recorded.

We assessed the safety and acceptability of the SWT in patients with chronic heart failure and examined the relationship between SWT performance and VO2 max. The protocol was approved by the local ethics committee and all patients gave informed consent. 50 men with established left ventricular dysfunction were referred from the Brompton Heart Failure Clinic for estimation of VO2 max. Mean age was 62.9 (SD 9.1) years and the mean VO2 max 17.9 mL/kg per min (range 6.8–39.1 [6.1]). These patients were subsequently evaluated with a SWT. All completed the test. Mean number of shuttles completed was 38 (range 4–102, SD 19). The SWT was well tolerated and, in a questionnaire administered after testing, 42 (84%) preferred the SWT, seven (14%) the treadmill test, and one patient had no preference (p < 0.0001 for the two groups with a stated preference). The main problems reported with the SWT were difficulties in turning and in accurate pacing.

The shuttle-walk test appears to be a safe and effective assessment of functional capacity in patients with heart failure. It does not require specialised equipment or facilities and can be done with several patients at the same time. It may have particular application in rehabilitation clinics or in the initial assessment and follow up of patients in units without cardiorespiratory exercise-testing facilities.


Association between VO2 max and number of shuttle walks completed

![Graph showing correlation between VO2 max and number of shuttle walks completed](https://via.placeholder.com/150)

The figure shows correlation between VO2 max and number of shuttle walks completed (r = 0.84, p < 0.0001). The calculated regression is VO2 max = (0.27 x number of shuttles) + 7.77, (r2 = 0.7). The 95% CI for the coefficient are 0.22 to 0.32 and for the constant 5.56 to 9.89.

The SWT appears to be a safe and effective assessment of functional capacity in patients with heart failure, which can be done with several patients at the same time. It may have particular application in rehabilitation clinics or in the initial assessment and follow up of patients in units without cardiorespiratory exercise-testing facilities.

Treatment of Tourette’s syndrome with mecamylamine
Paul R Sanberg, R Douglas Shytle, Archie A Silver

We have previously reported that nicotine potentiated the therapeutic actions of neuroleptic drugs in Tourette’s syndrome. 2, 3 Dursun et al 4 reported similar findings with nicotine, both in combination with haloperidol and alone. We now report in a retrospective case series review that a nicotine antagonist, mecamylamine, also improves the symptoms of Tourette’s syndrome. Mecamylamine is an antihypertensive agent that readily enters the brain and has broad inhibitory actions at several nicotinic acetylcholine receptor subtypes.

St Mary’s University College, Twickenham, Middlesex, and The Royal Brompton Hospital, London SW3 6NP, UK (R H Stables; e-mail r.stables@rbh.nthames.nhs.uk)
We have treated 13 Tourette's patients with mecamylamine in doses up to 5 mg daily. Four were adults (one female; mean age 34 years); nine were children (one female; mean age 14 yrs). 11 of the 13 patients receiving mecamylamine also reported an improvement in the Clinical Global Impressions - Severity of Illness (CGI-S). In seven of these patients with Tourette's syndrome, concomitant use of mecamylamine up to 5 mg daily reduced the severity of motor and vocal tics as assessed by the Yale Global Tic Severity Scale (YGTSS) (see table). Mecamylamine also appeared to help other symptoms of Tourette's syndrome, even when tics symptoms were unchanged. These improvements were quantified (table) by the CGI-S. Mecamylamine appears to help the non-tic behavioural symptoms associated with Tourette's syndrome, even when tics symptoms were unchanged. These improvements were quantified (table) by the CGI-S.

Wanted information: Effect of mecamylamine (MEC) in Tourette's syndrome in seven patients with follow-up information.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
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<th>Concomitant medications</th>
<th>MEC (mg/day)</th>
<th>Days at follow-up</th>
<th>YGTSS Before MEC</th>
<th>YGTSS After MEC</th>
<th>CGI-S Before MEC</th>
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Means (SEM) 44.4 (10.6) 23.6 (6.0)* 5 (0.44) 2.3 (0.18)*

*p<0.05 Wilcoxon signed rank test; significantly different from before MEC (mecamylamine)

Outbreak of meningococcal disease linked to a sports club
Yi Mien Koh, G Howard Barnes, Ed Kaczynski, James M Stuart

Seven cases of meningococcal disease occurred in a small town (population 7100) in West Yorkshire over a 2-month period from mid November, 1995. The attack rate was 99/100 000. The notification rate for meningococcal meningitis and septicemia in England and Wales during 1995 was 4/100 000. There were no deaths. One case was diagnosed clinically, two had serum antibody values consistent with recent meningococcal infection (one serogroup C, one serogroup undetermined), and in four cases serogroup C 2a P1.5 P1.2 strains were isolated from blood culture (table). Household contacts of each case were given prophylactic antibiotics with or without vaccine in line with recommended guidance for sporadic cases.1 Naphospharyngeal carriage of Neisseria meningitidis was surveyed in pupils at the schools with cases, the local high school, and one of the two local primary schools. In the high school, overall carriage rate among pupils in the same year as the three cases was 11% (16/146); in primary schools it was 2.5% (6/242). No carriers of the outbreak strain were identified. A community intervention was carried out among all 2–18 year olds who were resident in or attended school at the outbreak town. Of the estimated 2653 in this target group, 2219 (84%) received meningococcal A and C vaccine along with either a 2-day course of rifampicin or a single dose of ciprofloxacin.

Possible links between cases were investigated. The two main local social venues for teenagers were a youth club in the high-school grounds, and a rugby football and association football sports club. Six of the seven cases were either rugby players or linked to the sports club through friends or family members (table). Immediately before the community intervention, 56 out of 100 rugby players aged 11 to 18 years were swabbed. The carriage rate of N meningitidis was 29% (16/56), but no carriers of the outbreak strain were identified. Troat swabs were also taken from 400 individuals who had left school and who attended vaccination points; one teenage girl was found to be carrying the outbreak strain. She had a boyfriend (carriage status unknown) who played rugby at the sports club.
**Cases in community outbreak November, 1995-January, 1996**

In the 12 months after this outbreak, two cases caused by the outbreak strain occurred in brothers who were rugby-playing members of the sports club; a 19-year-old (May, 1996) who lived outside the town and had not been immunised, and his 17-year-old sibling (5 weeks later) who was at school in the town and had received vaccine and antibiotics at the time of the intervention. A third case (June, 1996) occurred in a 20-year-old woman resident without known links to the sports club.

Social links in clusters of meningococcal disease are uncommon but have been reported.6,7 There is a low carriage of serogroup C strains in outbreaks8 and our findings support a hypothesis that membership of the sports club was a risk factor for disease in this outbreak. In outbreaks of meningococcal disease, searching for a social network linking the cases is worthwhile and may be of more value than carriage studies in identifying populations at risk.


**Fetal exposure to maternal cortisol**

**Rachel Gitau, Alan Cameron, Nicholas M Fisk, Vivette Glover**

The relation between maternal and fetal cortisol has been disputed. Schwartz1 suggests that maternal cortisol contributes much to fetal cortisol concentration until the key events of parturition. By contrast, Benediktsdottir and Seckl11 state that high placental 11α-hydroxysteroid-dehydrogenase activity excludes maternal cortisol from the fetus in early and mid gestation, and that cortisol does not cross the human placenta readily at any stage. The studies cited do not, however, compare paired maternal and fetal concentrations. Previous studies of paired maternal-cortisol and fetal-cortisol samples have shown no significant correlation, but had narrow ranges of concentrations.

We measured plasma cortisol concentrations in paired maternal and fetal venous samples from blood taken for clinically-indicated fetal testing at 13–35 weeks’ gestation (n=43). All women signed informed consent, required by the institutional ethics committee. We excluded fetuses that were small for gestational age, had abnormal blood pH or partial pressure of oxygen, known major abnormalities, or aneuploidy. Maternal blood samples were collected immediately before the procedure and fetal samples within 10 min of needle entry, a time within which fetal cortisol is known not to rise.3 We assayed cortisol by standard radioimmunoassay. Mean maternal cortisol (547 [SD 316] nmol/L) was substantially higher than fetal values (53 [33·0] nmol/L), with a maternal/fetal ratio of 11·4 [7·0]. Maternal values ranged from 88 nmol/L to 1188 nmol/L and fetal from 13 to 184 nmol/L. Fetal concentrations were linearly related to maternal cortisol concentrations (r=0·62, p<0·001, figure 1). Neither maternal nor fetal concentrations correlated with gestational age (r=−0·02 and r=0·12, respectively).

Our data suggest that maternal cortisol may account for about 40% of the variance in fetal concentrations. Such association need not be causative and maternal and fetal cortisol concentrations may be controlled by independent factors, such as placental corticotropin-releasing hormone. Our finding is, however, also compatible with substantial (80–90%) metabolism of maternal cortisol during passage through the placenta. Thus, since fetal concentrations are much lower, a contribution of 10–20% from the mother, could still double fetal concentrations. A direct study of the maternal-fetal cortisol transfer in the fetal-placental unit before abortion6 showed 15% of 3H-cortisol crossed the placenta unmetabolised. This finding is consistent with 40–50% of fetal cortisol being derived from the mother. Schwartz7 and Benediktsdottir and Seckl11 may both be correct. There is metabolism of most of the cortisol passing through the placenta, but the maternal concentration may still have a major effect on the fetal concentration.

This correlation between maternal and fetal cortisol may help to explain how antenatal maternal stress affects the fetus, resulting in babies with lower birthweight and impaired brain development.9 Animal studies show that maternal stress during pregnancy can alter long term...
Symptomatic restenosis after carotid percutaneous transluminal angioplasty

Francesca Crawley, Andrew Clifton, Robert S Taylor, Martin M Brown

Carotid percutaneous transluminal angioplasty (PTA) for treating carotid stenosis is increasingly being used as an alternative to carotid surgery. One criticism of carotid PTA is that restenosis may be more common than after carotid surgery. Case series suggest that restenosis occurs in 7–16% of individuals after carotid PTA, but that it is usually symptomless. By contrast, coronary PTA is associated with a significantly higher requirement for reintervention than coronary-artery bypass grafting (38% vs 11% within 2 years of procedure). Restenosis after coronary PTA is histologically quite distinct from the appearances of atherosclerosis. Restenosis is associated with smooth-muscle proliferation, rather than the intracellular and extracellular lipid deposits and intimal foam cells that characterise atherosclerosis. Symptoms from stable coronary-artery disease are generally taken to be haemodynamic in origin, whereas most symptoms due to carotid stenosis are embolic. If restenosis after carotid PTA results in a smooth surface (as found after coronary PTA), embolic symptoms are unlikely. We describe the histological findings of restenosis after carotid PTA.

A woman aged 77 years presented with a right-hemisphere ischaemic stroke in February, 1996. Carotid dopplers and magnetic resonance angiography showed an 80–95% stenosis of the right internal carotid artery and complete occlusion of the left internal carotid artery. She made a full recovery. Angioplasty was performed in July, 1996. After systemic heparinisation, the stenosis was crossed with the wire and a balloon passed over the wire to lie across the stenosis. Atropine (0·6 mg) was given before balloon inflation. The balloon was inflated to a pressure of seven atmospheres for 10 s. During this time, the patient became hypotensive and bradycardic. Angiography performed after balloon deflation showed a residual stenosis of 70%. The patient was still hypotensive (blood pressure 90/50 mm Hg) and, therefore, balloon reinflation was not attempted.

14 months after carotid PTA the patient had a right-hemisphere transient ischaemic attack, with sudden onset of weakness of her left arm and leg after getting into a hot bath. Her symptoms resolved within 10 min of getting out of the water. Doppler showed that the stenosis was 80–95%.

Immunohistochemistry for smooth-muscle actin (brown) Tissue is cellular with spindle-shaped cells containing smooth-muscle actin arranged in haphazard crossing pattern, typical of accelerated smooth-muscle proliferation.

She elected to have carotid endarterectomy, which was performed in October, 1997. Pathologically, the plaque was composed of dense connective tissue with calcification. A few macrophages were present. Newer connective tissue with loosely arranged collagen was superimposed on the older plaque material. These areas of new connective tissue were rich in connective tissue proteoglycans and had a characteristic arrangement of smooth-muscle cells in a storiform pattern. These appearances were characteristic of accelerated smooth-muscle proliferation (figure).

The finding of smooth-muscle proliferation rather than recurrent atherosclerosis after restenosis is consistent with the hypothesis that this patient’s recurrent symptoms after carotid PTA resulted from haemodynamic rather than embolic mechanisms. The precipitation of the transient ischaemic attack by a hot bath strongly suggests that vasodilatation and relative hypotension decreased cerebral perfusion. Haemodynamic symptoms are uncommon in the cerebral circulation because of the collateral supply provided by the circle of Willis. In our patient, however, this mechanism is likely to have been deficient because her restenosis was severe and her contralateral internal carotid artery was occluded. Such severe impairment of collateral supply is uncommon and, assuming that most restenoses after carotid PTA have a similar pathology to our patient, may explain why recurrent symptoms are much rarer after carotid PTA than after coronary PTA.

Ultrasound B and blood pressure

Rolfdieter Krause, Malte Bühring, Werner Hopfenmüller, Michael F Holick, Arya M Sharma

Abnormalities of calcium homeostasis, possibly related to vitamin D$_3$, deficiency or increased concentrations of parathyroid hormone, may play a part in the development of essential hypertension. Although UVB irradiation is well known to affect vitamin D$_3$ production, its effect on blood pressure has not been much studied. 18 patients with untreated mild essential hypertension (8 women, ages 26 to 66 y) were randomised to receive thrice-weekly full-body UVB (Helarium lamps; spectrum 94.5% UVA, 3.5% UVB; Cosmedico GmbH, Stuttgart, Germany) or UVA (TL 10 lamps; spectral output 99.5% UVA, 0.05% UVB; Philips, Eindhoven, Netherlands) irradiation at suberythematos doses over 6 weeks (during February to March). Irradiation commenced with an exposure time of 6 minutes at 0.7 of the minimal erythmal dose (MED), and if tolerated was increased by 10% each subsequent treatment.

Ambulatory blood pressure (Spacelabs 90207/92; Spacelabs Inc., Redmond, Washington, USA) and plasma concentrations of 25(OH)D, 1,25(OH)$_2$D, and intact parathormone (iPTH) were measured before and after the irradiation period. The protocol of the study was approved by the institutional Ethics Committee. Intra-group comparisons were with the non-parametric Wilcoxon Test, while inter-group comparisons were performed with the Mann-Whitney U Test.

One patient dropped out of the UVA group for personal reasons and was excluded from analysis. UVA and UVB irradiation lowered blood pressure in both groups, although the results were not statistically significant. There were no significant changes in plasma vitamin D concentrations. 25(OH)D dropped significantly (p<0.01) in both groups, with no evidence of increased iPTH in the UVA group. The UVA group had lower blood pressure at 6 months (p<0.01).

Effects of UVB on blood pressure

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<th>Group</th>
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</table>

Before: ns, After: p<0.01.

Effect of UVB on blood pressure

Department of Dermatology, Mie University, School of Medicine, Mie 514-8507, Japan (H Mizutani; e-mail h-mizuta@clin.med.mie-u.ac.jp); Department of Dermatology, Ehime University, School of Medicine, Ehime; and Department of Dermatology, Nagoya University, School of Medicine, Nagoya.

Cultured epidermal-sheet graft for epidermodysplasia verruciformis

Hitoshi Mizutani, Yuji Shirakata, Ayumi Adachi, Koji Hashimoto, Masayuki Shimizu

Epidermodysplasia verruciformis (EV) is a rare skin disease due to persistent human papilloma virus (HPV) infection. Multiple cancerous lesions develop after middle age. EV lesions are resistant to interferon and immunotherapy, and require surgical treatment with skin grafts. The numbers of cancerous lesions increase annually, while donor sites for normal skin diminish. Banking of cultured epidermal sheets may resolve this problem.

A 50-year-old woman with EV complained of enlargement of Bowenoid cancer lesions on her face and forehead. Multiple lesions did not respond to intralesional interferon-α, interferon-γ, or bleomycin. Because she had had multiple surgical treatments, areas with normal skin suitable for grafting were limited. Two cm$^2$ of clinically normal skin distant from the Bowenoid cancers and warts was harvested after obtaining informed consent. Keratinocytes were cultured from the specimen and prepared as epidermal sheets. Multiple facial cancerous lesions were removed surgically. The raw surfaces where the tumours had been excised and split thickness skin graft donor site were covered with the cultured epidermal sheets using a fibrin adhesive. The sheets had adapted completely within a week. Grafted skin was amelanotic but there was no apparent recurrence of verrucous lesion observed during a 3-year follow-up.

To eliminate HPV infection in cultured epidermal sheets, HPV DNA was analysed by a PCR protocol specifically detecting tumorigenic HPV. DNA samples were prepared from a verruca plana lesion, two different BC lesions excised from the same patient and the cultured epidermal sheets. EV-related HPV DNA specific bands were amplified in both the samples from the BC lesions and verruca plana lesion the same as HPV-47 DNA control; no EV-related HPV DNA was detected in the cultured epidermal sheets. There was no relapse of the verruca for 3 years, which also supports the results of PCR analysis. Since there is no established curative treatment, a self-skin banking system may contribute to the treatment of EV.

groups were comparable in age (48 [26 to 66] yr, body-mass index (27·0· [24·4 to 31·8] kg/m²) vs 25·8 [22·0 to 38·5] kg/m²) and gender distribution (3 female / 5 male vs 4/6). Total irradiation time was 260 [250 to 261] min and 198 [109 to 261] min in the UVB and UVB groups, respectively. Cumulative vitamin D3-weighted irradiance dose in the UVB (9740 [5373–12807] J/m²) group was around 40 times higher than in the UVB group (227 [219–228] J/m², p<0·0001). Irradiation was well tolerated in both groups. Treatment caused a significant reduction in 24-h ambulatory systolic and diastolic blood pressure in the UVB (-8·6 to -1·1 to +1·2 to -2·2 mmHg, p<0·001) but not in the UVA group (0/2 [-1·0 to 3] mmHg). This fall in blood-pressure was evident both during daytime and night-time (figure). In the UVB group there was a 162% rise in plasma concentrations of 25(OH)D (57·6 [12·0–91·2] to 151·2 [100·8–273·6] nmol/L, p<0·001) and a 15% fall in iPTH (3·9 [2·9–6·7] to 3·3 [1·8–5·3] pmol/L, p<0·01), while in the UVA group, 25(OH)D (38·4 [12·0–72·0] to 45·6 [12·0–62·4] nmol/L) and iPTH (4·3 [2·9 to 7·3] to 4·5 [2·5 to 8·3] pmol/L, remained unchanged. Serum 1,25(OH)2D, calcium, and inorganic phosphate were not affected by irradiation in either group (data not shown).

Our study shows that serial whole-body irradiation with an artificial UVB source, in contrast with a UVB source, can reduce blood pressure in patients with untreated mild hypertension. Because 25(OH)D concentrations in a substantial number of participants in both groups were well below 50 nmol/L, recently suggested to indicate vitamin D insufficiency, and only UVB irradiation resulted in a normalisation of 25(OH)D concentrations, the blood-pressure-lowering effect may be mediated by concomitant changes in calcium-regulating hormones.

We thank K nut Grothmann and H einrich K ause, Institute for Lighting Technology, Technical University Berlin; Berhard K ratz, Hansipenter Schauff, and U like Schorr of the Universität-klinikum Benjamin Franklin; and to C A Chen of the Boston University Medical School. Funding was provided in part by the “Förderverein Sonnenforschung e.V.”, Stuttgart, Germany, and NIH grant M 01RR 00533 (M F H).

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Patient-detected diurnal changes in spleen volume

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A 37-year-old physician had a brief illness characterised by polyarthritides, fevers, and sweats. Examination showed generalised lymphadenopathy, moderate splenomegaly (4 cm in length from the splenic tip to the costal margin), but no hepatomegaly. Abdominal lymphadenopathy was noted on computed tomograph scanning. The diagnosis of follicular non-Hodgkin lymphoma was established after examination of a cervical lymph-node biopsy specimen and bone-marrow aspiration. After 3 months of watchful waiting he was treated with a monthly cycle of oral chlorambucil (10 mg daily for 10 days) and prednisolone (50 mg daily for 14 days). Because of increasing abdominal discomfort, probably the result of associated enlargement of his spleen, he began to palpitate his spleen daily and reported fluctuations in its size (of up to 2 cm in length from the splenic tip to the costal margin) at different times of the day. He also noted that this finding was accentuated when he took prednisolone.

To confirm the patient’s findings, computed tomograph (CT) scans were done at 8·15 and 17·30 on the same day with a GE HiSpeed helical scanner without oral or intravenous contrast. The patient took 50 mg of prednisolone immediately after the first scan. He had not been on chlorambucil for 18 days. He was positioned supine with arms resting above his head. Scans were on gentle arrested inspiration in order to minimise breathing misregistration. A scout film of the upper abdomen was done to localise helical acquisition and a helical series done through the spleen at 120 kV, 300 mA, with a pitch of 1·7:1 (20 s scan time), a 7 mm collimation and reconstruction at 7 mm intervals. The same operator conducted the two scans. Volume measurements were done on a GE Advantage Windows Workstation (ver 2·0·2), with a semi-automatic Volume Segmentation/Paintbrush utility to do the volume calculation. On each image the spleen was outlined by a hand-drawn trace and the software maintained a running total of the volume calculations.

Spleenic volume was 2335·38 mL in the morning and 1949·74 mL in the evening, a 16·5% reduction in volume over 10 h. This change in volume is much greater than can be explained by interobserver and day-to-day coefficients of variations of CT scans. The scan was repeated 2 months later under the same conditions, 18 days after a cycle of chlorambucil therapy (10 mg for 10 days). The spleenic volume was 2016·32 and 1765·06 mL in morning and afternoon, a 12·5% reduction.

Noradrenaline causes the spleen to contract by autonomic stimulation. Noradrenaline expression follows a circadian rhythm related to sleep. Melatonin production has also been shown to suppress noradrenaline. Concentrations of noradrenaline are lowest at night, allowing the spleen to engorge with blood and appear swollen in the morning. Noradrenaline is released during the course of a day causing the spleen to contract. This concentration is further amplified by taking corticosteroids which stimulate sympathetic activity. The magnitude of this diurnal variation in spleen size has not been previously reported. It is possible that this phenomenon may be going unnoticed in other patients with splenomegaly. If management decisions are based on the size of the spleen, diurnal variation could have an impact on decisions made. It is important that repeated spleenic measurements are made at the same time of day.

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